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MINI REVIEW

Expanded principles of ethics and its implementation during COVID-19 vaccine trials: A scoping evidence based research synthesis

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ABSTRACT

The COVID-19 pandemic will subside only through the emergence and distribution of an efficacious vaccine. The two main aspects that should be maintained in equilibrium: the dire necessity for speedy vaccine research and the need for safeguarding the research subjects, which is of utmost concern in research ethics. This opens up a discussion of what norms to follow during the clinical trials while developing the vaccine. As of now, various companies like Moderna, Pfizer, University of Oxford, Astra-Zeneca and so on have moved beyond the safety, efficacy and immunogenic studies. This narrative review explores and discusses the key principles of ethics: a principle of autonomy, beneficence, non-maleficence, and justice along with its ten general expanded principles. Furthermore, it delves into the different types of vaccines, their mechanisms, side effects, limitations, and advantages.

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Introduction

The worldwide escalation in the cases of the coronavirus disease (COVID-19) throws light on the dire requirement for an efficacious, safe COVID-19 vaccine. In September 2020, the Advisory Committee on Immunization Practices put forth four main interim ethical principles, essential for development and implementation of recommendations for COVID-19 vaccine use, including maximization of benefit for the patient, to do no harm, equality, justice and fairness.[1] The rapid spread of the pandemic necessitated an acceleration in obtaining a vaccine, this demand has become critical for all medical professionals and scientists even though it might include a more 'relaxed' approach in order to establish procedures.[2]

The Global Solidarity Trials began in February 2020, an initiative by the World Health Organization (WHO) research forum in order to recommend evaluation for treatments in large and randomized trials on COVID-19 disease.[3]

Although there are differences, a few common value orientations including autonomy, beneficence, non-maleficence, justice and confidentiality have to be followed by medical professionals.[4,5] A strong emphasis on these ethical principles and the ability to negotiate differences may be advantageous not only to the patients but also the health-care professionals.[6] Besides, multiple vaccine applicants are being involved at an increased tempo with the aim of slowing down the global pandemic of COVID-19, the disease resulting from SARS-CoV-2, a novel coronavirus. Therefore, bioethicists should prompt selections that weigh the immediacy of the outcomes of the catastrophe with ethical practice.[7] This mini-review article focuses on ethical considerations during the COVID-19 vaccine trials along with its expanded principles and the significance of them. Also, it renders a brief overview of various vaccines.

Materials and methods

This mini-review conducted a thorough literature search in published peer reviewed journals. The search was done utilizing articles in PubMed database using the above-mentioned keyword. The combination of the following terms was used "ethical principles followed during COVID-19 times," "principle of autonomy," "Beneficence," "Justice and Non maleficence." There were around 879 articles found after the search, out of which the relevant references summed up to a total of 34. The screening process of the references was done by the authors and about 34 references pertinent to the "Expanded principles of ethics and its implementation during COVID-19 vaccine trials" were included in this review. This research was conducted from January to March 2021.

Results

Autonomy

Autonomy is pivotal in bioethics. Autonomy simply implies respect for persons. It ensures that subjects are capable of making their decision which is recognized, respected and at the same time safeguarding the autonomy of the vulnerable by avoiding unnecessary decisions. This fundamental principle gave rise to informed consent which is now practiced legally wherein qualified subjects or an authorized candidate is permitted to decide to take part in a study or not. Informed

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consent must subsume a well thought out process for achieving the goal of research and it is expected to be complied to.[8]

Moreover, some researchers concur that autonomy is extremely crucial and that there are situations where a person's own choice should be valued about their treatment although others might be in a better place to decide for the well-being of the patient.[9]

The question arises, on what basis informed consent is considered invalid? When researchers themselves give the wrong description of research either due to lack of knowledge or understanding? Is it done deliberately due to their false belief? Or are the volunteers misguided by researchers? The factors such as ignorance and uncertainty make it difficult to obtain a valid informed consent. Therefore, in the present scenario of understanding and knowledge, validity is of serious concern for the participant's consent to COVID-19 vaccine trials.[10]

The COVID-19 vaccine trials' informed consent forms are not available publicly because of privacy reasons.[11] These informed consent forms are similar to the "Risks to participants" part of the trial protocols which have been given by Pfizer, Moderna and Johnson & Johnson in the vaccine trials for COVID-19.[12] These three vaccines represent the diverse vaccines that are being tested.

In addition, all of these three protocols include the risk of any diseases associated with or by administration of the vaccine. The mentioned risks in the consent form for Moderna vaccine are after allergy reaction at the site of injection, fainting, systemic adverse events and laboratory abnormalities. For Pfizer vaccine, the risks mentioned are local site injection reactions and systemic adverse reactions. For Johnson & Johnson, risks such as phlebotomy and collection of nasal swab samples are present. Lastly, Moderna and Pfizer, cite the risk of prior proof of vaccine-elicited disease enhancement with Respiratory Syncytial Virus (RSV), dengue and also feline coronavirus for Pfizer whereas it is measles for Moderna. The side effects, limitation, mechanism of action and advantages of the various vaccines are mentioned in Table 2. The informed consent form must explicitly mention the protocol and related risks of worsened COVID-19 virus from the inefficiency of the vaccine up to death if any.[9]

Beneficence

Beneficence is of central value in ethics in medical trials. It states that researchers should do good for the patients enrolled in the study. It is a moral obligation, in which researchers do things for the benefit of participants by preventing them from any harm.

Beneficence can be subdivided into actual benefits and perceived benefits. In actual-benefit, patients may have an extra advantage for financial compensation or additional medical assistance. Actual-benefit rarely changed in COVID-19 clinical trials. However, perceived benefits have a foreseen medical outcome for a newfound treatment for the vaccine and are likely to change.[13]

Moreover, WHO issued "Human challenge trials" to speed up the COVID-19 vaccine trials without undergoing phase III trials, where volunteers were deliberately infected to develop COVID-19 vaccine.[14] It questioned an important ethical principle which is, beneficence. Is it fair to infect people on purpose with deadly coronavirus infection, knowing the consequences?[15] Furthermore, it is tough to elucidate the durability of COVID-19 vaccine with phase I or phase II trials. Also, re-infection registered with SARS coronavirus. Without any evidence on the immune response to COVID-19 vaccine, verification on durability and "beneficence" is questionable.[16] In order to do good, the expedited vaccine trials should prioritize the protection of human being. Different technologies carried out in the development of vaccine research. Out of the different technologies carried out in the development of vaccine research, mRNA and DNA-based vaccine techniques are imposed on the trial applicants. mRNA vaccine possesses the risk of Interferon response like inflammation and autoimmune disorders; DNA-based shows plausibility to trigger mutagenic effect. The scientist will know about these possible risks only at the later stage of the trial.[17] Before administering any vaccine, it is crucial to weigh the risk and the benefits. Research revealed that Pfizer and Moderna are efficacious in protecting severe COVID-19 and are likely to stop the spread too.[7]

Non maleficence

Non-maleficence is a principle that demands no subject should be harmed during the process of the study. This principle ensures that the study conducted and the design of the study must minimize any possibility of harm, given the chance of limited benefit for all those participating in the study.[18,19] The probability and severity of harm to the subjects should be addressed by risk mitigation.[8]

Potential maleficence can be broadly categorized into risks and burden. In normal instances, the volunteers participating in clinical trials are subjected to risks that are unknown and serious adverse effects of the procedure. For a study participant, the additional risks might involve that the new treatment method is ineffective or the treatment may not be as good as the standard treatment that was being followed or may be a subject assigned in group that did not receive any active treatment (control group participant).[13]

In the COVID-19 vaccine trial, there are two significant ways where the participant might be subjected to potential risk. Firstly, the risk of contracting SARS-CoV-2 because of increased exposure to others. Secondly, a drug that is still under investigation could increase the likelihood of contracting SARS-CoV-2 or might even worsen the symptoms and outcomes of COVID-19. The risk of contracting the virus can be due to three reasons: 1) presence of asymptotic virus carriers at the time of the study trail. 2) The virus effective reproduction number. 3) To reduce the risk of contamination, strategies implemented by trail-specific risk mitigation. The transmission of SARS-CoV-2 by an asymptotic carrier is still being debated.[13]

The direct transmission of virus can be protected by following norms like social distancing, regular sanitization protocols, application of personal protective equipment and screening of SARS-CoV-2 before confinement. In case of an individual being infected, compartmentalization should be done to

prevent spread of virus to the population at large. This can be done by separation of regular care from trials, isolation of infected individuals, utilizing different areas of the clinic for class confinement or performing home visits. These methods aid in mitigating the risks and can be scaled up or down based on the population under study and the dynamic of the virus to increase non-maleficence without being a burden on the subjects.[13]

Careful consideration must be given to vulnerable participants with life threatening conditions as they are highly susceptible to infection when participating in the clinical trial during the pandemic. Thus, the added benefit should be thoroughly weighed against the potential factors that can cause harm for COVID-19 morbidity and mortality.[13]

The strategies for risk mitigation should be identified so that it can be carried out during the pandemic. Apart from the risk of being infected with SARS-CoV-2, complications of the virus for the particular study population should be carefully examined and weighed. Geriatric patients and any person with underlying comorbidities like hypertension, diabetes mellitus, chronic lung disease and cardiovascular diseases are at an increased risk of severe COVID-19 disease. There also might be a requirement of ICU admittance and mortality.[13]

The risk analysis on investigational compound should be carried out highlighting the additional risks of SARS-CoV-2 and has to be added to every investigational study record file until the COVID-19 pandemic persists, as these are recommended by the present EMA (European Medicine Agency) and FDA (Food and Drug Administration) COVID-19 guidelines.[13]

Finally, the impact of the pandemic on the burden for the study subjects should be taken into consideration. The side effects that are expected, discomfort and anxiety related to participation in the study or study procedures, study restrictions, challenges related to traveling to the clinic, investment of time and findings related to the health status of the patient all include in the burden for the study participants. The strategies of risk mitigation as discussed like social distancing further increase the burden on the participant. Lack of certainty related to trail continuation during a new viral outbreak can cause anxiety in patients, for example, in oncology patients.[13] Thus, only necessary risk mitigation strategies should be implemented in order to decrease the burden on study participants and should be immediately put to an end when redundant and not automatically maintained till the end of trial. Since millions of citizens received either Moderna or Pfizer vaccines, a few serious adverse effects were shown such as anaphylactic reactions, and thrombocytopenia. Anaphylaxis were revealed by people allergic to any previous medication or vaccine. Overall, scientists have not been able to conclude if thrombocytopenia was due to the vaccine.[7] Also, there were cases of myocarditis, heart inflammation in a few young male adults.[20]

Justice

Justice, which is the final principle of bioethics, acts on fair judgment. It is sub-categorized into 1) distributive justice, 2) justice-related to subject's right, 3) legal justice.[13]

Distributive justice states that there should be fair delivery of limited resources to people at large. Due to high demand and less production in an unprecedented situation like the COVID-19 pandemic which makes the distribution difficult or sometimes impossible. The foremost role of the vaccine is to lower the infection and minimize the spread in the community. During the vaccine distribution, people at high risk should be prioritized first. Proponents claim that herd community with a denser population, poor citizens and lack of medical facilities should get the vaccine delivered before others. In local areas; immunocompromised, comorbidity, old age and poor patients should be prioritized whereas globally; the underdeveloped and developing countries that lack in sanitization, have scarce availability of food and water, that are at greater risk of health hazards should be pondered. Although the distribution of COVID-19 vaccine in the developing countries seems difficult, it is not impossible.[21,22] When the COVID-19 pandemic began, there was an increase in the influx of patients in the health-care system globally. As a result, other non-acute health-care activities including clinical trials were postponed. The shortage of medical staff, equipment, protective equipment, test kits and intensive care units due to the COVID-19 pandemic soon led to the cessation of clinical trials. Therefore, when allocating limited resources, a method should be used that provides the maximum benefit to all patients, be it COVID-19 or other diseases.[13]

The right of subjects includes protection from misconduct or negligence, medical care provision, compensation for damage, medical confidentiality, privacy of data and its protection, right to participate freely in the study trial and right of withdrawal whenever during the clinical trial.[13]

Legal justice refers to respect to a morally acceptable law. Although clinical trials are standardized, it was during the COVID-19 outbreak that additional instructions were released by European Medical Agency (EMA), US Food and Drug Administration (FDA) and several national health authorities.[13] These new instructions need time, analysis to be implemented and is open to discussion. It was over challenging initially due to the coronavirus urgency. Thus, it is essential to continue an open discussion between clinical sites, sponsor and ethics committee for application in a clinical trial. Unless guidelines for data integrity and subject safety are followed, mutual decisions can be acceptable. It is observed that at times sponsors take an aberrant path to continue trials for potentially fatal conditions where a trial needs to be put on hold. In this situation, it is necessary to record any decisions taken explicitly and their justification if there is any deflection because of the COVID-19 pandemic.

Discussion

The four major ethical principles namely; autonomy, justice, non-maleficence, and beneficence are all woven together into the conduct of vaccine trials. The principle of autonomy is explicitly evident while communicating with people and their communities. This principle is crucial before, after, and during a vaccine trial while simultaneously being aware of traditions, concerns, and sensitivities. Beneficence signifies that an effective product of the

vaccine will benefit the individuals participating in the study. Non-maleficence ensures that the adverse reactions and/or any complications of the vaccine should be mentioned in the extensive scheme. Lastly, justice assures that the benefits and hardships of research for developing a vaccine will be delivered and distributed with utmost fairness. Furthermore, the basic ethical principles are expanded to ten general principles which include the principle of essentiality. The principle of voluntariness, informed consent and community agreement: the research applicant should be notified about the study and plausible risk-benefit. The principle of non-exploitation; principle of privacy and confidentiality; Principle of precaution and risk minimization: Applicant or others affected by the study are exposed to minimum risk, or no irreparable adverse reaction; Principle of professional competence. The principle of accountability and transparency: study should be justified and completely disclosed by the researcher. The principle of maximization of public interest and distributive justice; the principle of the public domain; the principle of the totality of responsibility: the study should be surveilled and evaluated at all stages (Table 1).

Further, SARS-CoV-2 necessitated global partnership and teamwork to battle against it, such that multiple vaccine candidates from varied countries can render a high-range and faster delivery of the vaccine to generate world "herd immunity." Both BioNTech/Pfizer and Moderna are utilizing vaccination technologies using nucleic acid-based mostly vaccines that have not nevertheless progressed on the far side of clinical trials for previous diseases. Additionally, Inovio and Zydus Cadila produce nucleic acid; however, unlike Moderna and BioNTech/Pfizer, process DNA instead of RNA. Sinovac Biotech and Sinopharm specify inactivated shape of the virus.[28]

Additional details about different vaccines are depicted in Table 2.

Recent trends

Emergency use authorization (EAU) is a measure utilized during a global health crisis such as the coronavirus pandemic. EUA facilitates the use of medical countermeasures like vaccines. COVID-19, an unprecedented outbreak, called for expedited vaccine trials to curb the disastrous scenario. Relatedly, questions arose regarding the duration required to develop a vaccine without it having adverse effects. The FDA (Food and Drug Administration) declared that an average observation of two months is required after at least half of the individuals have been inoculated with their final dose before authorizing the vaccine for emergency use. Moreover, there is immense concern portrayed by the FDA, that by granting EAU, it would further impede long-term evaluation of efficacy and safety, which might lead to the vaccine creators not obtaining sufficient data for a license to market their vaccines.[29] In general, it is beneficial to approve administering vaccines to high-risk and susceptible individuals that have met their final dose and still shown no proof of complications after the two months. However, studying these vaccines comprehensively is the need of the hour to optimize the guidelines on dosage and efficient delivery in the time to come.[7] The Central Drugs and Standards Committee (CDSCO), a drug regulator in India, promulgated an urgent approval for Covaxin on 3rd January 2021, although phase III trials are still underway, and there are unpublished phase II studies.[30] The indigenously generated Covaxin was in "clinical trial mode" due to lack of sufficient data to facilitate its full authorization. This clinical trial label, which had

Table 1. Expanded principles of ethics in COVID-19 research trials.

Principles	Ethical consideration in COVID-19 research trials
Principle of essentiality	It must be reviewed by an independent and responsible person who, after careful consideration, must decide that research can ease humankind.[23]
Principle of voluntariness, informed consent and community agreement	People participating must be briefed about the right to refrain or withdraw from the study at all times. Principle of voluntariness, informed consent applies to the entire society and each individual where the study requires treating anyone in the society.[23]
Principle of non-exploitation	The participants should be completely informed of all potential risks that may occur during research. Also, each participant should be compensated by any insurance or other means for any expected or unexpected risks and provide therapeutic and comprehensive post-operative aftercare.[23]
Principle of privacy and confidentiality	The database and identity of the participants should be kept confidential to prevent any form of suffering and inequity.[23]
Principle of precaution and risk minimization	Risk minimization can be promoted by selecting patients who are both young and healthy, and by giving them priority access to top-notch medical facility during the trial. Current, SARS CoV-2 Controlled Human Infection (S-CHI) includes additional risk minimization rule and improved consent processes aimed at fostering participants, accepting possible dangers.[24]
Principle of professional competence	Healthcare workers should fully understand both the practical and moral rationale for authorizing COVID-19 vaccine.[25]
Principle of accountability and transparency	The principle of transparency is enforced across the entireness of vaccine allocation decision making process. This principle, decision making process and design of COVID-19 vaccine allotment must be evidence-based, explicit, comprehensible and publicly available.[26]
Principle of maximization of public interest and of distributive justice	The distribution of the COVID-19 vaccine should promote equity by knowingly ensuring that everyone has an equal chance of being vaccinated, both in the groups recommended at the start of vaccination and when the vaccine is available instantly.[26]
Principle of public domain	The research result must be in the public domain and provide access to any production facility that promises to operate under strict international control.[27]
Principle of totality of responsibility	This principle states that the research should be rightfully observed and must be subjected to review consistently along with the medicinal action being taken at each point.[23]

Table 2. Comparison of different COVID-19 vaccines.

Vaccine	Mechanism of action	Advantages	Adverse effects	Limitation
Moderna, Pfizer, BioNTech	RNA vaccine of RNA encapsulated within a LNP to decrease RNA degradation and increase translation efficiency.	The translation of mRNA occurs in the cytosol of the host cell averting the risk of any sort of integration into the host genome.	Pain, Fever, Fatigue and Headache.	Reports of safety issues with reactogenicity have been noted. Also shows instability.
Astra-Zeneca, CanSino	Viral vector vaccine that encapsulates the genome of different weakly pathogenic virus with additional DNA that encodes the target viral antigen.	The host may possess immunity against the vector due to prior exposure, reducing the efficacy. May lead to cancer due to the integration of the viral genome into the host genome.	Pain, Headache and Chills.	Show a highly specific gene delivery into the host cell with a vigorous immune response. Avoids handling of any infectious particle and it has been used widely for Middle East respiratory syndrome coronavirus MERS-CoV with positive results from the trials.
Zydus Cadila	DNA Vaccine using a DNA plasmid that encodes a target antigen, often administered by electroporation.	It can be developed at an accelerated pace. It does not require the handling of the infectious viral particle.	N/A	It might induce antibody production against itself.
Novavax	Incorporates subsection of the native virus such as a S protein.	Do not have any live component of the viral particle. Thus, it is safe with fewer side-effects.	Pain, Headache and Fatigue.	Induces an immune response Memory for future response is doubtful
Codagenix, Ankara	Live attenuated vaccine (LAV) that can replicate, but in a limited manner that cannot cause the disease.	It has the intrinsic ability to stimulate the immune system by inducing the toll-like receptors (TLRs) namely: TLR 3, TLR 7/8, and TLR 9 of the innate immune system that involves B cells, CD4 and CD8 T cells. It can be derived from 'cold adapted' virus strains, reassort ants, and reverse genetics.	N/A	There is a requirement of extensive accessory testing to establish safety and efficacy.
Sinovac, Sinopharm (Inactivated)	Inactivated vaccine that uses the native virus that rendered replication deficient from heat or chemical treatment.	Stable and safer as compared to the LAVs. Has already been tested for SARS-CoV and various other diseases. It can be used along with adjuvants to increase their immunogenicity.	N/A	Booster shot required to maintain immunity.

inadequate data and the requirement of informed consent, bred a sense of hesitancy in the uptake of the vaccine. Government is liable for compensation related to vaccine-induced injuries during clinical trials; however, there are no such norms post-licensure roll-out. Recently, the data on its efficacy showed promising results thereafter, Covaxin has shed its label of "clinical trial mode," making it available as an effective vaccine (efficacy rate = 81%) against the novel coronavirus.[31,32]

An unscrupulous deed practiced by the People hospital in Bhopal during these troubled times that breached the principle of non-maleficence was witnessed. The disadvantaged residents were misled to thinking that they were vaccinated outside trial whereas enrollment was for phase 3 clinical trial. The participants were allured a prize money of Rs 750 each. Coincidentally, the residents enrolled were the survivors of 1984 gas tragedy. Many of the trial participants encountered debilitating adverse effects which they were uninformed about.

Similar to various forms of vaccines and vaccine elements, there are different intellectual property rights (IPRs) germane to vaccines. For example, there is a debate going on regarding the ethical implications of according rights (patent) for technologies that provide health benefits, like vaccines. The major contributor to vaccine production is derived from public funds. Hence, the innovator companies are not threatened if the IPRs are subverted.[33] Relatedly, to achieve global normality, efficient COVID-19 vaccines must be accessible to everyone at the earliest.[34] Waiving the IPRs will largely boost vaccine uptake all around the world, ensuring global access and bringing about equity.

Conclusion

Currently, the world is undergoing the development of the COVID-19 vaccine with trepidation. Therefore, after an efficient vaccine is developed, the stakeholders must address the ethical issues that come along its way. Needless to say, even in such catastrophic situation the urgency of offering a vaccine must be balanced by exigency of investigation in ethics for the better of mankind. The need of the hour is to broaden a safe and competent COVID-19 vaccine that could set off the proper immune reaction to break off the chain and safeguard subjects at all costs during the trials, especially the vulnerable ones.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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